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ORIGINAL RESEARCH

Real-World Analysis of Potential Drug-Drug Interactions with Nirmatrelvir/Ritonavir Based on the Hospital Prescription Analysis (HPA) Database in 9 Cities of China

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Purpose: To determine the real-world patterns and extent of potential drug-drug interactions (DDIs) related to nirmatrelvir/ritonavir (NMVr) in China.

Patients and Methods: Data on NMVr-treated patients from over 160 hospitals across 9 Chinese cities from January 2022 to December 2023 were extracted from the Hospital Prescription Analysis (HPA) database, which was established in Beijing in 1997 to promote rational medication use in China. Grade C, D and X DDIs from the Lexicomp database were defined as clinically significant and analyzed in this study. Statistical analyses included descriptive statistics (continuous variables as mean ± SD; categorical variables as counts and percentages) and multivariate binary logistic regression, which was used to identify factors associated with potential DDIs, with adjustment for confounding variables (sex, age, cities, number of co-administered drugs, comorbidities). Analyses were performed using R software (v4.2.2) with $P < 0.05$ as statistically significant, and figures were generated via GraphPad Prism (v10.3.1).

Results: Of 15,567 patients receiving NMVr, the mean age was 62.4 ±18.2 years, and 53.1% were male. 8542 patients received at least one co-administration, and 5391 patients exhibited at least one potential DDI. A total of 10,694 potential DDIs were identified, with a breakdown of 8310 grade C, 2093 grade D and 291 grade X. Systemic corticosteroids (n=3608) and drugs for obstructive airway diseases (n=2220) had the highest frequencies in grade C DDIs, and the lipid modifying agents (n=601) in grade D DDIs, and cardiac therapy drugs (n=130) in grade X DDIs. Co-administration of drugs significantly increased odds of potential DDIs with the risk escalating markedly as the number of drugs increased, and the comorbidities of hypertension (odds ratio [OR]=1.50), asthma (OR=4.28) and mental disorders (OR=7.02) significantly increased it as well.

Conclusion: In this large-scale cross-sectional study in China, approximately one-third of the patients treated with NMVr were at risk of clinically significant potential DDIs, highlighting the importance of making efforts to diminish these risks, such as close monitoring and dose adjustment.

Keywords: NMVr, DDIs, coronavirus disease-2019, COVID-19, patient safety

Introduction

Nirmatrelvir Tablets/Ritonavir Tablets (co-packaged) acquired conditional approval from China in February 2022 as a potent antiviral treatment. It has been widely used during the coronavirus disease-2019 (COVID-19) pandemic in China. However, since ritonavir has a significant influence on the activities of drug-metabolizing enzymes and transporters, such as cytochrome P450 (CYP) 3A4, CYP2D6, and P-glycoprotein transporters, it may lead to clinically meaningful drug-drug interactions (DDIs) with other co-medications.[1]

Several case reports have documented DDIs associated with nirmatrelvir/ritonavir (NMVr), all with significant clinical consequences. Jiang et al reported a 32-year-old male with systemic lupus erythematosus who developed acute

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nephrotoxicity and neurotoxicity with supratherapeutic tacrolimus level after resuming tacrolimus 5 days following self-administration of NMVr, and his tacrolimus concentration was reduced with phenytoin (a CYP3A4 inducer) effectively under pharmacist guidance.[2] López-Hernández et al reported a case of a 71-year-old immunosuppressed male with COVID-19 pneumonia and invasive aspergillosis, in whom concurrent use of NMVr and voriconazole led to a significant increase in voriconazole plasma concentration accompanied by hypertransaminasemia. Voriconazole was then temporarily discontinued and restarted 2 days after the 10-day NMVr course, with concentrations remaining within the therapeutic range thereafter.[3] Rauser et al reported a case of a 79-year-old woman with stage 4 chronic kidney disease, hypertension, and other comorbidities. After 3 days of NMVr treatment for COVID-19 during concurrent nifedipine use, she developed extremity edema, oliguria, and acute kidney injury. Discontinuation of both agents resulted in resolution of edema and normalized renal function within 2 days; subsequent outpatient follow-ups showed good tolerance to nifedipine without NMVr.[4] Casey et al reported a case of a 70-year-old female with multiple comorbidities who developed ranolazine toxicity after 5 days of concurrent use of NMVr and ranolazine, presenting with obtundation, bradycardia, and hypoxia. The patient recovered to baseline over 54 hours after drug discontinuation with supportive care.[5]

Several studies have attempted to illustrate the prevalence of these DDIs in the real-world,[6–8] but large-scale investigations were limited. Gerhart et al screened the top 100 prescription medications using the Optum Clinformatics Data Mart database in the US and found that NMVr might cause potential DDIs with 30 of the top 100 drugs. However, this research only provided a general profile of these DDIs without more in-depth information such as the prevalence of these DDIs.[9] Another cross-sectional study involved 37,767 outpatients receiving NMVr mentioned the potential DDIs without detailed information as well.[10] Xiao et al conducted a cross-sectional study on potential DDIs related to NMVr, involving 3214 adults in the United States.[11] However, large-scale research of this kind is still lacking in China.

This study aimed to reveal the real-world patterns and extent of potential NMVr-related DDIs based on a nationwide database in China for the better management of these DDIs in the future.

Materials and Methods

The Hospital Prescription Analysis (HPA) program database was established in Beijing, China, in 1997, aiming to promote the rational use of medications in Chinese hospitals. It randomly collects 10-day de-identified prescription data quarterly from outpatients and inpatients during workdays in more than 160 participating hospitals across nine cities, including Beijing, Chengdu, Guangzhou, Hangzhou, Shanghai, Tianjin, Zhengzhou, Shenyang, and Harbin in China, enabling researchers to conduct numerous studies.[12,13] Each prescription includes the following information: hospital's regional location, date, patient encrypted code, age, sex, department visited, diagnosis, generic drug name, dosage, usage, and cost.

Prescriptions of patients receiving NMVr from January 2022 to December 2023 in the HPA database were included in this study. The detailed inclusion criteria were (i) prescriptions containing NMVr issued between January 2022 and December 2023 and (ii) concurrent prescriptions for the same patients as those containing NMVr. The exclusion criteria were (i) prescriptions with missing information and (ii) prescriptions with anomalous data (eg, age exceeding 120 years). The HPA program has authorized the use of these data.

Potential DDIs were identified using the Lexicomp database. Lexicomp is a comprehensive drug information database that provides detailed information on drug-drug, drug-food, and drug-disease interactions. It has been widely used by healthcare professionals to identify and manage potential DDIs, including NMVr.[14–16]

Lexicomp classifies drug interactions into five grades. Among these, grade X (avoid combination) DDIs mean risks outweigh benefits, and their combination should be avoided. Grade D (consider therapy modification) DDIs suggest that physicians should conduct a patient-specific assessment and targeted actions to balance risks and benefits. Grade C (monitor therapy) DDIs indicate that benefits often outweigh risks but necessitate monitoring and potential dosage adjustments. In this study, grade C, D, and X DDIs were thus recognized as having clinically significant interactions. In contrast, grade A (no known interaction) and grade B (no action needed) DDIs were not included in this study.

Descriptive statistics were used in our study. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as counts and percentages. Multivariate binary logistic regression was used to identify factors

associated with potential drug-drug interactions, with adjustment for confounding variables including sex, age, cities, number of co-administered drugs, and comorbidities. Data were analyzed using R software (version 4.2.2), and a P - value < 0.05 was considered statistically significant. The statistical figures in this study were generated using GraphPad Prism (version 10.3.1) software.

Results

Baseline Characteristics

The prescriptions of 15,567 patients receiving NMVr were collected; Hangzhou had the highest proportion (25.5%), followed by Shanghai (24.1%), Guangzhou (11.8%), Beijing (10.8%), Shenyang (6.4%), Harbin (6.4%), Zhengzhou (5.8%), Tianjin (5.8%), and Chengdu (3.2%). Baseline patient characteristics are shown in Table 1. The mean (SD) age of these patients was 62.4 (18.2) years, and 53.1% were male. The three most common comorbidities were malignancy (8.5%), cardiovascular disease (5.6%), and hypertension (5.2%).

Prevalence of Potential DDIs

Among the 15,567 patients who received NMVr, 8542 patients received at least one co-administration. A total of 5391 patients exhibited at least one potential DDI, including 2182 patients with one potential DDI, 1596 with two DDIs, 851 with three DDIs, and 762 with more than three DDIs. The frequency and percentage of the top 20 potential DDI-involved drugs in each grade are shown in Table 2, and all potential DDI-involved drugs demonstrated in the anatomical therapeutic chemical (ATC) classification are shown in Figure 1. A total of 10,694 potential DDIs were identified, with a breakdown of 8310 grade C, 2093 grade D and 291 grade X. Systemic corticosteroids (n=3608) and drugs for obstructive airway diseases (n=2220) had the highest frequencies in grade C, and in grade D they were lipid modifying agents (n=601) and psycholeptics drugs (n=400) with cardiac therapy drugs (n=130) in grade X. Furthermore, Figure 2 described the age-based distribution of the frequency of drugs involved in potential DDIs classified under the ATC system.

Figure 3 shows the fluctuations in the number of patients receiving NMVr and the potential DDI prevalence rate during the investigated two years. As none of the patients received NMVr in the 1st and 3rd quarters, they were not included in this figure. The prevalence of potential DDIs has increased to 44.68% by the 1st quarter of 2023. However, when the number of patients receiving NMVr reached the top 8011 in 2nd quarter of 2023, the prevalence of DDIs

Table 1 Baseline Characteristics of NMVr Recipients Included in This Study

Variable	Value (N = 15,567)	
Age, mean (SD), y	62.4	(18.2)
Male, no. (%)	8263	(53.1%)
Comorbidities, no. (%)		
Malignancy	1325	(8.5%)
Cardiovascular disease	875	(5.6%)
Hypertension	808	(5.2%)
Diabetes	492	(3.2%)
Cerebrovascular disease	400	(2.6%)
Transplantation	208	(1.3%)
Chronic kidney disease	196	(1.3%)
COPD	170	(1.1%)
Mental disorders	152	(1.0%)
Autoimmune diseases	131	(0.8%)
Nervous System disorders	104	(0.7%)
Asthma	44	(0.3%)

Abbreviation: COPD, chronic obstructive pulmonary disease.

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Table 2 Frequency and Percentage of the Top 20 Potential DDIs Involved Drugs in Each Grade

Grade C			Grade D			Grade X		
Drugs	**Frequency**	**% of total Potential DDIs**	**Drugs**	**Frequency**	**% of total Potential DDIs**	**Drugs**	**Frequency**	**% of total Potential DDIs**
Methylprednisolone	2082	19.47%	Atorvastatin	455	4.25%	Amiodarone	76	0.71%
Dexamethasone	1444	13.50%	Nifedipine	240	2.24%	Ivabradine	54	0.50%
Budesonide	1305	12.20%	Clopidogrel	225	2.10%	Tolvaptan	38	0.36%
Theophylline derivatives	828	7.74%	Fentanyl	222	2.08%	Nimodipine	17	0.16%
Amlodipine	498	4.66%	Voriconazole	200	1.87%	Garlic	16	0.15%
Lidocaine	292	2.73%	Midazolam	191	1.79%	Domperidone	16	0.15%
Calcitriol	253	2.37%	Rosuvastatin	146	1.37%	Fosaprepitant	12	0.11%
Beclomethasone	208	1.95%	Alprazolam	100	0.94%	Ticagrelor	12	0.11%
Zolpidem	159	1.49%	Digoxin	56	0.52%	Rupatadine	11	0.10%
Butorphanol	97	0.91%	Felodipine	52	0.49%	Salmeterol	7	0.07%
Olanzapine	79	0.74%	Zopiclone	46	0.43%	Rifampin	6	0.06%
Rivaroxaban	72	0.67%	Quetiapine	33	0.31%	Doxorubicin	4	0.04%
Valproate products	70	0.65%	Eszopiclone	28	0.26%	Carbamazepine	4	0.04%
Morphine	53	0.50%	Sufentanil	15	0.14%	Orelabrutinib	3	0.03%
Diazepam	49	0.46%	Cilostazol	14	0.13%	Phenobarbital	3	0.03%
Doxazosin	49	0.46%	Erythromycin	12	0.11%	Fusidic acid	3	0.03%
Tramadol	46	0.43%	Trazodone	9	0.08%	Simvastatin	3	0.03%
Cortisone	41	0.38%	Clarithromycin	7	0.07%	Vincristine	3	0.03%
Hydrocortisone	41	0.38%	Solifenacin	7	0.07%	Lercanidipine	2	0.02%
Codeine	40	0.37%	Tolterodine	7	0.07%	St john's wort	1	0.01%

declined to 31.78% and was maintained at a slightly lower level in the next two quarters. Figure 4 further reveals the fluctuations of drugs in ATC classification and DDI grades. The drugs with the highest DDI prevalence rates in grade C, D, and X were systemic corticosteroids, lipid-modifying agents, and cardiac therapy, respectively.

Factors with Higher Odds Ratios of Potential DDIs

Multivariate binary logistic regression was performed to determine the odds ratios (OR) of potential DDIs (Figure 5). The odds of potential DDIs increased significantly as the number of co-administered drugs increased, while those from Shenyang (OR=1.56), Zhengzhou (OR=1.72), Harbin (OR=2.02), and Tianjin (OR=2.67) had higher OR than those from Beijing. Among comorbidities, malignancy (OR=0.62) and diabetes (OR=0.63) were associated with significantly lower ORs of potential DDIs, whereas hypertension (OR=1.50), asthma (OR=4.28), and mental disorders (OR=7.02) significantly increased the ORs of potential DDIs. In addition, the age group of 0–17 years had a lower OR of 0.51 compared to the 18–59 years group. No other variables had a significant influence on the ORs of potential DDI.

Discussion

We found that the overall potential DDIs prevalence was approximately 30%, with the exception of 44.68% in the 1st quarter of 2023, and systemic corticosteroids were the most frequently involved drugs. Co-administration of drugs significantly increased the odds of potential DDIs, with the risk escalating markedly as the number of co-administrations increased, while hypertension (OR=1.50), asthma (OR=4.28), and mental disorders (OR=7.02) also significantly increased the ORs.

The prevalence of potential DDIs declined to 31.78% after reaching a maximum of 44.68% in the 1st quarter of 2023 and then remained stable. There was a surge in COVID-19 cases from December 2022 to February 2023 in China, with a considerable proportion of patients believed to be critically ill patients.[17,18] Since corticosteroids were recommended for serious cases,[19–21] the proportion of corticosteroids showed the highest frequency. Thus, the prevalence of potential DDIs may be driven by corticosteroid use. This was confirmed by similar changes in the proportion of corticosteroids. Because of the irreversible

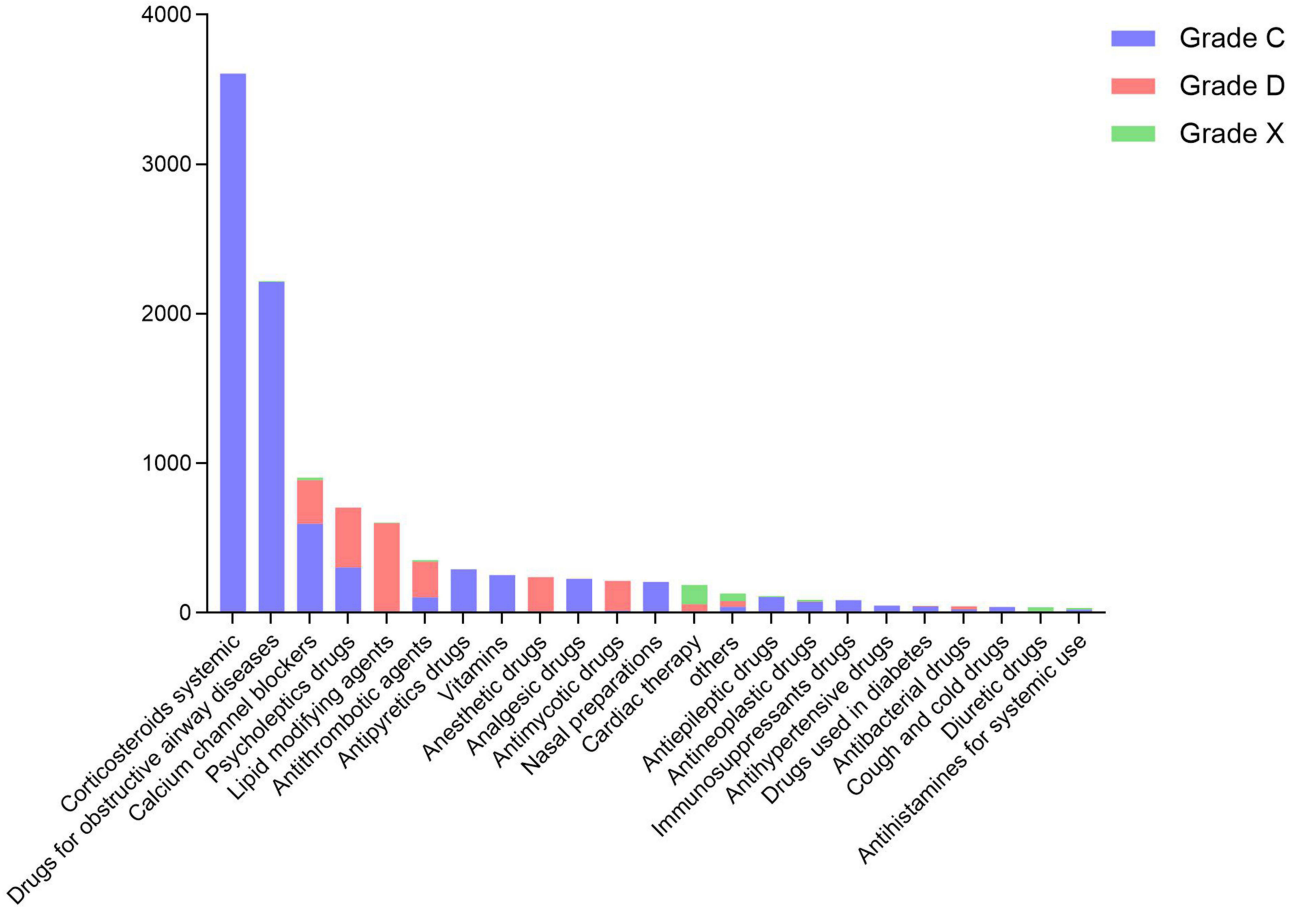

Figure 1 Grades and frequencies of ATC classifications for potential DDIs in NMVr recipients across 9 Chinese cities.

inhibition of CYP3A4 by ritonavir, practitioners should pay attention to adverse drug reactions due to the increased serum concentrations of corticosteroids, most of which are substrates of CYP3A4, when co-administered with NMVr.[1]

The DDI incidence rate of drugs for some chronic diseases, such as lipid-modifying agents, antithrombotic agents, and calcium channel blockers, has declined since 4th quarter of 2022. Since NMVr was conditionally approved by China in February 2022, and its first large-scale use was with the surge of COVID-19, there might not have been enough time for practitioners to be familiar with the DDIs of NMVr, especially considering the scale of DDIs and the surge scenario. After a short period of adaptation with the knowledge of NMVr-related DDIs spreading, the incidence declined even with many more patients compared with the initial use. Similarly, the information gap might also explain the variation in OR between cities.

Previous research has revealed that elderly people tend to have more DDIs due to polypharmacy for multimorbidity.[11,22–24] However, age did not seem to have a significant impact on potential DDIs with NMVrs in our study. This might be because co-administration was an independent factor considered in the multivariate logistic regression; therefore, age would not represent polypharmacy as an intermediate variable.

Co-administration significantly increased the OR of potential DDIs, which was consistent with previous studies. However, the extent of the OR increase in this study was much higher than that in previous studies. Research focusing on polypharmacy revealed that each of the five co-administrations increased the OR value by approximately 5 to 10 times and that of ten co-administrations can reach approximately 15 to 30 times.[25–28] However, we found that each co-administration contributed to an OR increase of approximately 10 times on average, and the value of more than ten co-administrations was 185.55. This indicated that patients with NMVr faced a much higher risk of potential DDIs than overall drugs. In the Lexicomp database, 523 NMVr-related DDIs, including grade C, D, and X, were documented, a number much higher than that of other drugs.

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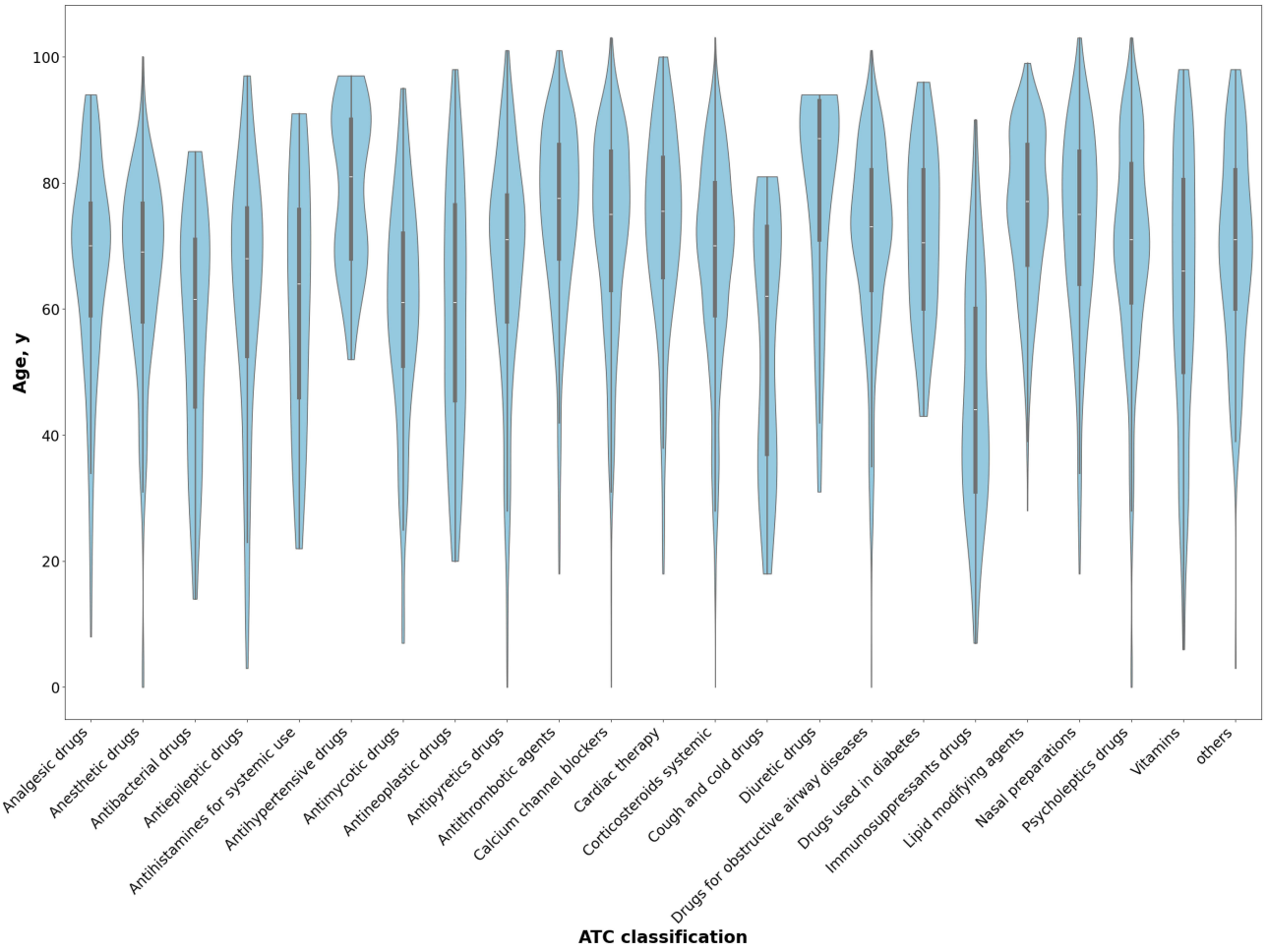

Figure 2 Age distribution of potential DDI frequencies by ATC-classifier drugs in NMVr recipients across 9 Chinese cities.

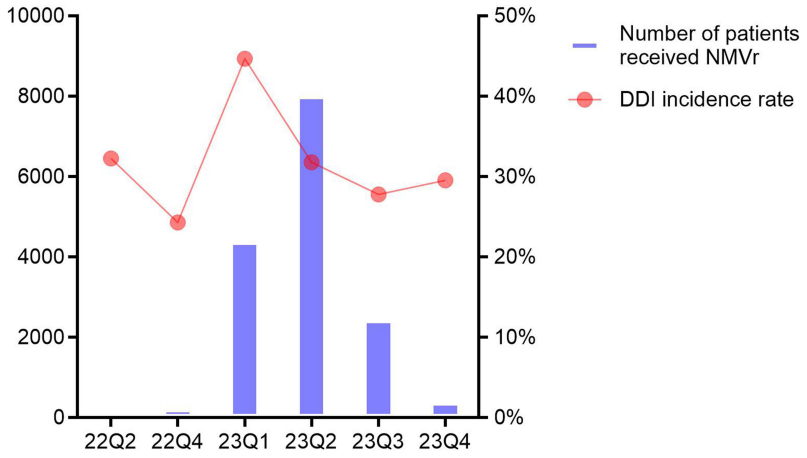

Figure 3 Fluctuations in the number of NMVr-treated patients and prevalence of potential DDIs (Q1 2022–Q4 2023).

Furthermore, drugs with higher odds of DDIs with NVMr, such as methylprednisolone, dexamethasone, budesonide, and theophylline derivatives, are widely prescribed for COVID-19 patients.[19–21]

A previous study in the US found that solid organ transplant patients were more likely to have a higher OR (3.63) of potential DDIs with NMVr.[11] However, we found that drugs for diseases including hypertension, asthma, and mental

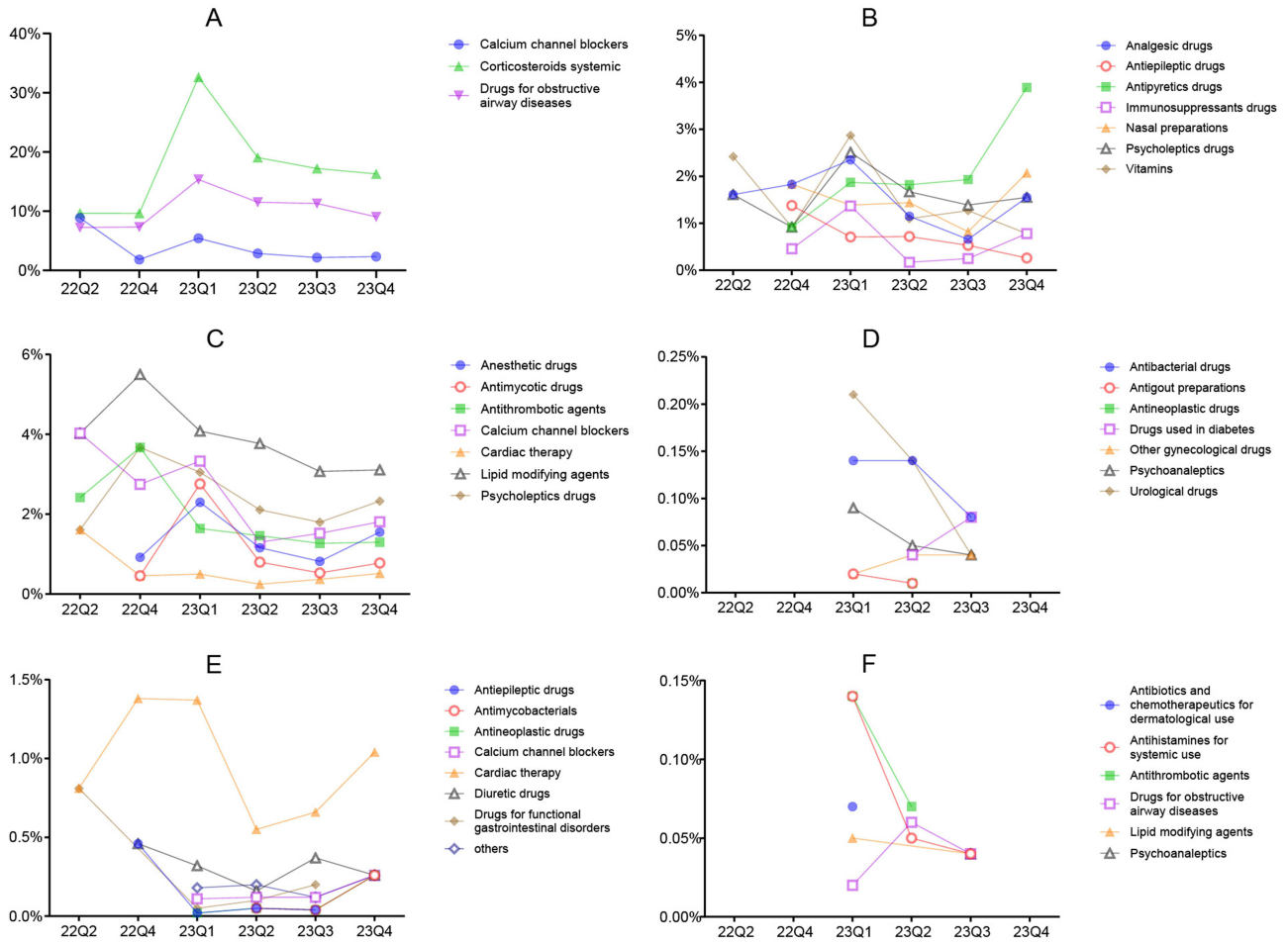

Figure 4 Fluctuations in potential DDI prevalence by ATC classification. (**A**) Grade C, >5%; (**B**) Grade C, 1%–5%; (**C**) Grade D, >0.5%; (**D**) Grade D, ≤0.5%; (**E**) Grade X, >0.2%; (**F**) Grade X, ≤0.2%.

disorders showed a high potential DDIs frequency, which corresponded to their elevated ORs, while transplantation showed a tendency to increase the odds without significance. In contrast, we found that drugs for malignancy and diabetes had a relatively low frequency, with lower odds. These results are consistent with the frequency of ATC classification of potential DDI-involved drugs. Furthermore, these findings suggest that the pattern might be independent in China, and could be the result of multiple factors, such as patient composition, accessibility of NMVr, progress of the epidemic, and epidemic prevention policy.

This study had several limitations. Firstly, the 10-day quarterly snapshot sampling strategy of the HPA database may underrepresent chronic medication use, particularly given the long-prescription policies allowing extended refill intervals for chronic conditions in China. This could lead to underestimated ORs for potential DDIs associated with chronic diseases such as malignancies and diabetes and limit our ability to assess the DDI risks from long-term co-administration. Additionally, though the database captures key prescription details, it lacks clinical data (eg, laboratory results), medication adherence and follow-ups, restricting evaluations of the actual clinical impact of identified DDIs.

Secondly, despite including nine cities, the generalizability of findings to other regions in China may be constrained because of variations in prescribing practices.

Thirdly, our identification of clinically significant DDIs, defined based on Lexicomp's standardized C/D/X classifications, has limitations: the database lacks clinical data (eg, laboratory results), and many Lexicomp-documented interactions are theoretical speculations that omit individual factors (eg, comorbidities, renal/hepatic function). Thus, the actual clinical impact

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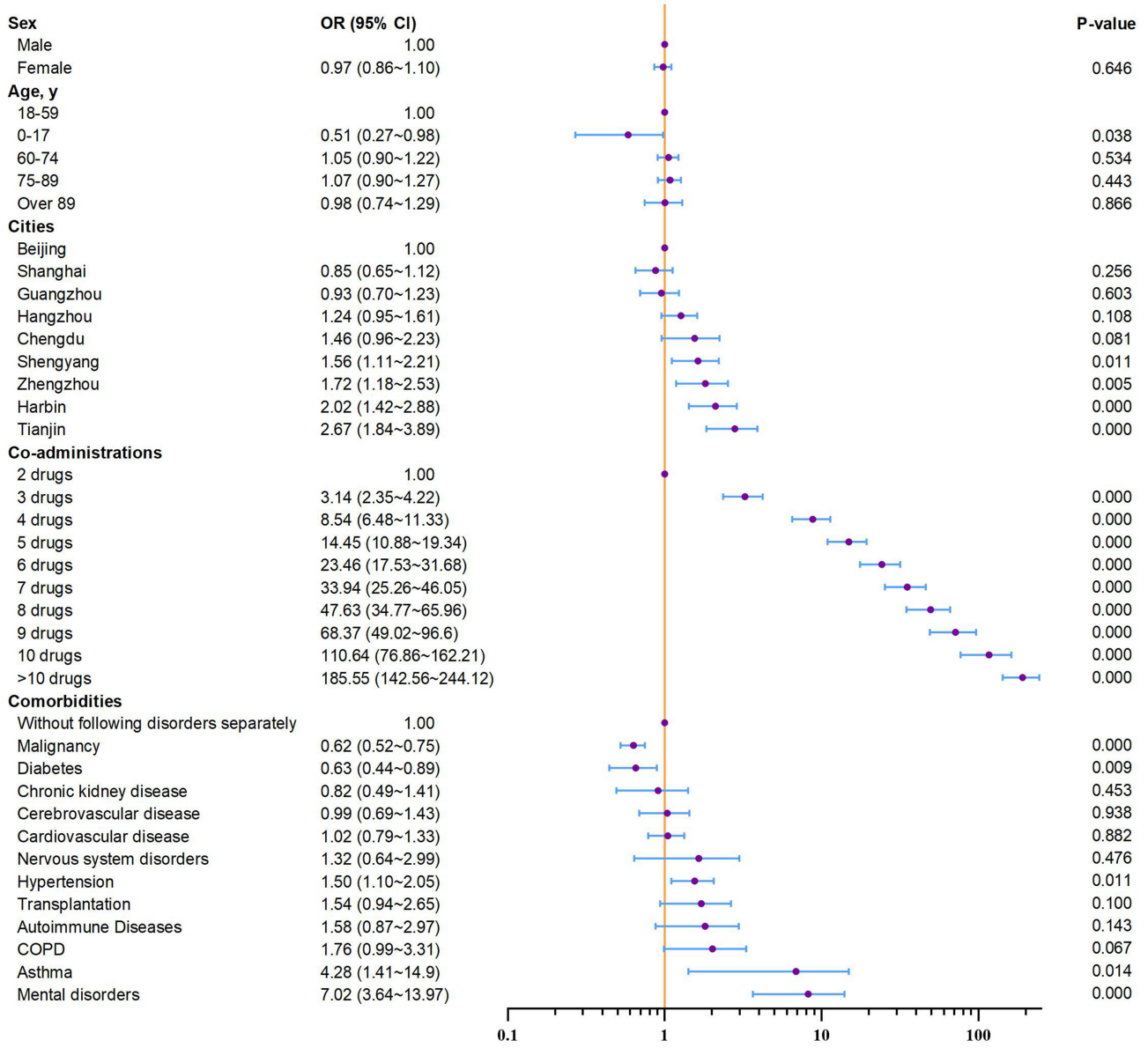

Figure 5 Associations between sex, age, cities, co-administrations, comorbidities, and potential DDIs, as estimated by multivariate binomial logistic regression.

of these DDIs requires further validation. Moreover, our screening of DDIs was based on the Lexicomp database as it was at the time of the study, and as the database undergoes subsequent updates, our findings may also require revision.

Finally, potential interactions between NMVr and traditional Chinese medicines, which were widely used during the pandemic, were not captured in Lexicomp, and related research remains scarce.

Conclusion

Based on data from China's HPA program, we found that approximately one-third of patients treated with NMVr were at risk of clinically significant potential DDIs, which were defined as grade C, D, and X in the Lexicomp database. Moreover, the risk increased significantly with the growing number of co-administered drugs, as well as specific comorbidities and regions. These findings underscore the critical need for corresponding proactive risk assessment and management strategies to mitigate NMVr-related DDIs according to the potential risk and severity, thereby enhancing medication safety in clinical practice.

Ethics Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital (KS2024130). The Ethics Committee waived the requirement for informed consent given the following exemption criteria: 1. The privacy and personal identity information of subjects were safeguarded; 2. Tracing remaining stored samples to individual patients or obtaining informed consent would have entailed significant waste of human and material resources, and the project does not involve personal privacy or commercial interests. As the author's affiliated hospital is a participating member of the HPA program—which explicitly permits data sharing among participants—the program has authorized the use of this data.

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Disclosure

The authors report no conflicts of interest in this work.

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